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FULL-LENGTH ORIGINAL RESEARCH

Potential for improved retention rate by personalized antiseizure medication selection: A register-based analysis

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Abstract

Objective: The first antiseizure medication (ASM) is ineffective or intolerable in 50% of epilepsy cases. Selection between more than 25 available ASMs is guided by epilepsy factors, but also age and comorbidities. Randomized evidence for particular patient subgroups is seldom available. We asked whether register data could be used for retention rate calculations based on demographics, comorbidities, and ASM history, and quantified the potential improvement in retention rates of the first ASM in several large epilepsy cohorts. We also describe retention rates in patients with epilepsy after traumatic brain injury and dementia, patient groups with little available evidence.

Methods: We used medical, demographic, and drug prescription data from epilepsy cohorts from comprehensive Swedish registers, containing 6380 observations. By analyzing 381 840 prescriptions, we studied retention rates of first- and second-line ASMs for patients with epilepsy in multiple sclerosis (MS), brain infection, dementia, traumatic brain injury, or stroke. The rank of retention rates of ASMs was validated by comparison to published randomized control trials. We identified the optimal stratification for each brain disease, and quantified the potential improvement if all patients had received the optimal ASM.

Results: Using optimal stratification for each brain disease, the potential improvement in retention rate (percentage points) was MS, 20%; brain infection, 21%; dementia, 14%; trauma, 21%; and stroke, 14%. In epilepsy after trauma, levetiracetam had

the highest retention rate at 80% (95% confidence interval [CI] = 65–89), exceeding that of the most commonly prescribed ASM, carbamazepine ($p = .04$). In epilepsy after dementia, lamotrigine (77%, 95% CI = 68–84) and levetiracetam (74%, 95% CI = 68–79) had higher retention rates than carbamazepine ($p = .006$ and $p = .01$, respectively).

Significance: We conclude that personalized ASM selection could improve retention rates and that national registers have potential as big data sources for personalized medicine in epilepsy.

KEYWORDS

big data, comorbidity, epidemiology, personalized medicine

1 | INTRODUCTION

The first tried antiseizure medication (ASM) is ineffective or intolerable in 50% of cases.[1] While ASM selection is influenced by the type of epilepsy and patient characteristics such as age and other medical conditions,[2] previously tried ASMs also provide clues, as drugs with similar modes of action tend to have similar efficacy and side effects.[3] After a trial-and-error process, two thirds of patients can eventually achieve seizure freedom.[1] There is seldom enough information beforehand on which ASM will be most effective in the individual patient. Personalized medicine, a concept referring to the prediction of treatment effectiveness based on the characteristics of an individual patient, is not yet possible but greatly needed in epilepsy.[4-8]

The challenges posed by the complexity of ASM selection are well recognized, and selection algorithms have been developed based on expert opinions.[3,9,10] Real-world data on ASM effectiveness would be of complementary benefit, but collection of long-term randomized evidence is difficult, especially for particular subsets of patients. Most clinical trials in epilepsy have heterogeneous populations with regard to comorbidities and age, follow patients for a few months, and evaluate adjunctive therapy in patients with drug-resistant epilepsy.[11] Real-world longitudinal data of ASM use and the ability to select narrow patient populations for prognostication is therefore needed. To address these challenges practically, we have previously used the Swedish drug prescription register to describe ASM retention rates in epilepsy after stroke and demonstrated concordance between our register-based real-life data and data from randomized controlled trials in the same patient group, showing the potential in the immediate clinical use of models derived from register data.[12-15] How to provide personalized therapy in epilepsy based on prediction of treatment effectiveness for a particular individual, however, remains an unsolved issue. Such predictions would need data and prediction algorithms incorporating multiple factors. Whether national registers of health and prescription data offer enough information to be useful for improving ASM selection is not known.

We analyzed retention rates of ASM in several Swedish population-based cohorts of focal epilepsy with a simultaneous brain disease—a situation with many ASM options. By stratifying patients optimally with regard to age, sex, and brain disease, we quantified potential for improvement of retention rates, had all patients been given the best first-line ASM for their stratum. We also described ASM retention rates in posttraumatic epilepsy and dementia, common forms of epilepsy where data to guide treatment are scarce.

Key Points

- ASM retention rates were calculated in cohorts with epilepsy after stroke, trauma, multiple sclerosis, dementia, and brain infections based on national register data
- The calculated retention rates were similar to retention rates in randomized controlled trials
- If patients had been given the optimal ASM with regard to sex and age, the retention rate of the first ASM could potentially be 14%–21% higher
- Previously used ASMs provide information about the retention rate of the next ASM
- We conclude that register-based statistics could provide complementary information to expert ASM selection algorithms in personalized medicine in epilepsy

2 | MATERIALS AND METHODS

2.1 | Registers

The study is based on datasets originally compiled from comprehensive national Swedish registers: the National Patient Register (NPR), Drug Register (DR), Cause of Death Register (CDR), Swedish Stroke Register, SVEDEM (national dementia register), and SMSreg (national multiple sclerosis [MS] register). The NPR is a register of all contacts with hospital-based out- or inpatient care in Sweden and was started in 2001, with complete coverage from 2005. Reporting to the NPR is mandatory for all health care providers in Sweden. The DR started on July 1, 2005 and contains information on all pharmacy-dispensed prescriptions in Sweden. The CDR contains information on all dates of death and causes of death. All registers are linked by personal identification numbers unique to each Swedish inhabitant.

2.2 | Study population

We included participants identified in previous cohort studies on acquired epilepsy after different brain diseases: MS, brain infection, dementia, trauma, or stroke (Table 1).[16] These datasets represent a population with probable focal onset seizures. The underlying brain diseases represent population-wide materials with regard to different etiological subgroups (Table 2).

In these studies, epilepsy was defined as the occurrence of the International Classification of Diseases, 10th Revision (ICD-10) code G40 in the NPR, except for the stroke cohort where, to comply with the current International League Against Epilepsy (ILAE) definition of epilepsy, all seizure-related diagnostic codes (G40, R568, G41) occurring more than 7 days after the initial stroke were considered evidence of epilepsy.

We included individuals from the above datasets with the first diagnosis of epilepsy after the start of the DR on July 1, 2005, which allowed us to track the entire ASM history. The specific inclusion criteria were a diagnosis of epilepsy as defined in the original cohort studies, the first diagnosis of epilepsy after July 1, 2005, and the first prescription of a valid ASM after the first seizure. The combination of an ICD-10 code for epilepsy and the prescription of an ASM is highly specific for epilepsy in administrative data.[21] Patients were excluded if they died within 60 days of their brain disease diagnosis to minimize impact of acute symptomatic seizures and avoid artificially increased retention rates on commonly selected first treatments. Patients with two or more ASMs dispensed within 7 days of initial treatment start were excluded to avoid effects of initial polytherapy on the retention rate for a single treatment. The inclusion and exclusion steps are illustrated in Figure 1A.

The datasets were anonymized by the National Board of Health and Welfare, and therefore we cannot exclude that some patients could exist in several cohorts because of multiple brain diseases prior to epilepsy. The inclusion and exclusion criteria resulted in a dataset of 6380 observations in total.

2.3 | ASM tracking

All prescriptions of ASMs (defined as Anatomical Therapeutic Chemical code N03) for the included individuals were identified, resulting in a dataset of 381 840 dispensations. We defined ASM start as the first dispensation date. Patients were followed until death or the end of the DR data. The retention rate was calculated by Kaplan–Meier (KM) analysis, and confidence intervals (CIs) were calculated using Greenwood's exponential formula. Swedish prescriptions are valid for 1 year, and each dispensation is usually sufficient for 3 months of use.[22] Discontinuation was defined as more than 12 months without a new prescription and set at 3 months after the last dispensation. The same algorithm has been used previously to describe first-line ASM use in the MS[23] and stroke datasets.[24] Dispensations of gabapentin, pregabalin, and clonazepam are frequently used for other indications than epilepsy and were therefore considered invalid.

TABLE 1 Study dataset

Dataset	Start year	End year	*n*	Female, %	AEDs, *n*, median (max)	Age at epilepsy onset, years, median (range)
MS	2005	2015	149	66	1.70 (6)	50.5 (18–81)
Infection	2005	2018	243	55	1.71 (9)	59 (19–93)
Dementia	2007	2018	699	55	1.23 (4)	81 (47–98)
Trauma	2005	2018	265	35	1.49 (6)	61 (18–94)
Stroke	2005	2015	5024	45	1.33 (7)	76 (18–100)
Total	2005	2018	6380	46	1.35 (9)	75 (18–100)

Note: The number of patients with epilepsy for each preexisting brain disease in the dataset is shown.

Abbreviations: AED, antiepileptic drug; MS, multiple sclerosis.

TABLE 2 Etiologies of brain diseases

MS	60.4% relapsing–remitting MS 29.3% secondary progressive MS 8.9% primary progressive MS 1.4% progressive relapsing MS
Brain infection	47.7% other meningitis 7.8% abscess 7.3% tick-borne encephalitis 3.7% herpes simplex virus encephalitis 10.3% other encephalitis
Dementia	28.4% Alzheimer disease, onset at >65 years 3.4% Alzheimer disease, onset at <65 years 22% unspecified dementia 19% mixed Alzheimer disease and vascular 19% vascular 2.2% dementia with Lewy bodies 1.6% frontotemporal dementia 1.5% Parkinson disease 2.8% other type of dementia
Trauma	68.2% mild injury 14.7% extracerebral injury 7.8% diffuse cerebral injury 5.4% fracture 3.8% focal cerebral injury
Stroke	87.3% ischemic stroke 9.6% intracerebral hemorrhage 3.1% unspecified stroke

Note: Subjects are from the following cohort studies: MS,[17] brain infection,[18] dementia,[19] trauma,[20] and stroke.[16]

Abbreviation: MS, multiple sclerosis.

The analyses are visualized in the supplemental material. Individual study cohorts can be selected based on brain disease, and delimited with regard to sex and age at epilepsy onset. If two ASMs were dispensed within 7 days, the medication was considered polytherapy, and the patient was not included in the analysis of either of the ASMs. Retention rates were only estimated if at least 10 individuals using the same ASM were available. Second-line ASM was defined as strictly the second ASM used by the patient. The second-line ASM could be used simultaneously as the first-line ASM as long as the usage started at least 7 days after the first ASM. Probability values comparing retention rate curves with one ASM in each curve were calculated using a $\log(-\log(\cdot))$ test[25]; the procedure for obtaining probability values for the optimal retention rate is described in the next section.

2.4 | Calculation of optimal retention rate

To calculate the potential for improvement we explored the optimal stratification for each brain disease regarding sex or no sex split, and different splits by age. The age splits were (no age split), (60), (70), (80), (50, 80), (40, 60, 80), (60, 70, 80, 90), (40, 50, 60, 70, 80, 90). The optimal stratification was found by Kaplan-Meier (KM) curves of the ASMs with the highest 5-year retention rate for each assessed stratum, and events in this curve were integrated into a new KM curve, which was compared to all other ASMs combined. The stratification set with the largest difference in the 5-year retention rate was considered optimal. If the retention rate of an ASM was not available at 5 years, the latest available retention rate was used as an estimation. To test if the difference between the highest retention rate ASMs and the other ASMs was significant, we adapted an unbiased cluster test[26] since using a regular test could inflate the Type I error. Each stratum's retention rate was considered as a data point, and the highest retention rate ASMs and the other ASMs were each considered as a cluster ($\widehat{\mathscr{C}_1}$ and $\widehat{\mathscr{C}_2}$, respectively). The p-value is defined as $p = \mathbb{P}\left(\phi \geq x^T\hat{v}_2 | \widehat{\mathscr{C}_1}, \widehat{\mathscr{C}_2} \in \mathscr{C}\left(x'(\phi)\right)\right)$ where x is a data point, $\phi \sim \left(\sigma\|\hat{v}\|_2\right) \cdot \chi_q$, and $\hat{v}$ is the contrast coefficients defined by $\hat{v}_i = 1\left\{i \in \widehat{\mathscr{C}_1}\right\} / \left|\widehat{\mathscr{C}_1}\right| - 1\left\{i \in \widehat{\mathscr{C}_2}\right\} / \left|\widehat{\mathscr{C}_2}\right|$. $\mathscr{C}$ is the clustering function, $\mathscr{C}$ is a cluster, and χ_q is the chi-square distribution with q degrees of freedom, corresponding to the number of features in the data. Here, retention rate is the one feature of the data, meaning $q = 1$. σ is the standard deviation of the data points. We used the mean weighted by the number of patients of the standard deviation for each data point, $\sigma = \frac{\sum_i^X \omega_i p_i}{\sum_i^X p_i}$. X is the set of all data points, ω is the greenwood

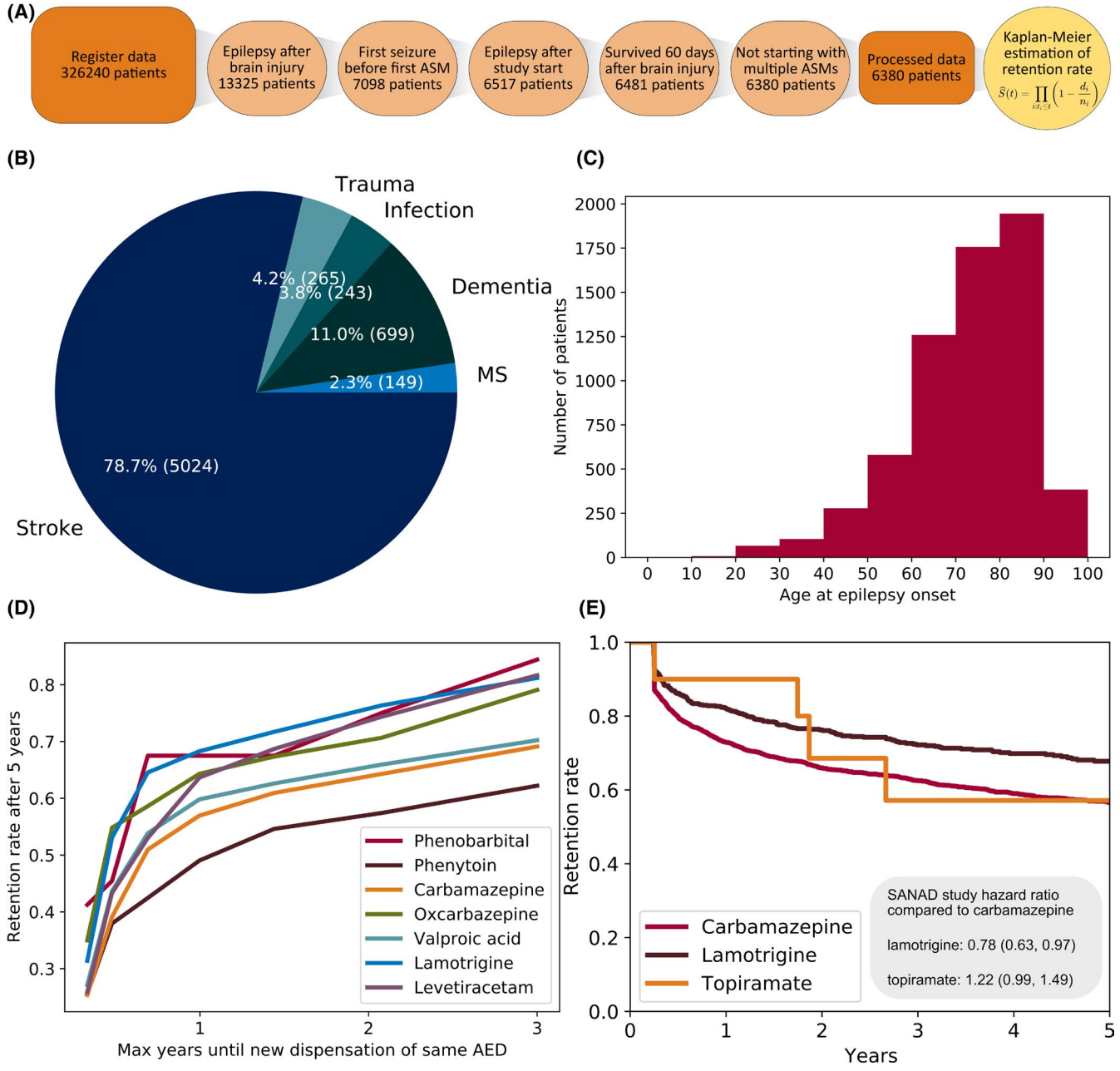

FIGURE 1 (A) Flow chart of data processing. (B) Proportions of datasets. (C) Distribution of epilepsy onset age. (D) Validation of the time intervals in the algorithm; sensitivity analysis of the 5-year retention rate (y-axis) of antiseizure medications (ASMs) when the grace period (x-axis) is changed. The greatest effect on retention rates was seen with increasing the grace period to 1 year, which is a point from where the rank of ASMs becomes stable while the retention rate is kept from being artificially high. (E) Comparison to the randomized trial SANAD showed similar 5-year retention rates: lamotrigine, 68% (95% confidence interval [CI] = 64–71); topiramate, 57% (95% CI = 22–82); carbamazepine, 57% (95% CI = 54–59). Carbamazepine was the most common ($n = 3020$, 47%) followed by lamotrigine ($n = 775$, 12%) and lastly topiramate ($n = 10$, <1%). SANAD study hazard ratios compared to carbamazepine: lamotrigine, .78 (95% CI = .63, .97); topiramate, 1.22 (95% CI = .99, 1.49).[27] Hazard ratio greater than 1 indicates that the retention rate is lower. AED, antiepileptic drug; MS, multiple sclerosis

variance, and p is the number of patients. $x'(\phi)$ is x perturbed by ϕ and $\widehat{\mathscr{C}_1}, \widehat{\mathscr{C}_2} \in \mathscr{C}\left(x'(\phi)\right)$ is the set of all valid ϕ where the clusters do not switch data points. In this case, the upper bound is infinite and the lower bound of the perturbation is the difference between the mean of the clusters and the minimum difference in retention rate between a highest retention rate ASM and its corresponding other ASMs for the same stratum, $\left\{\phi: \widehat{\mathscr{C}_1}, \widehat{\mathscr{C}_2} \in \mathscr{C}\left(x'(\phi)\right)\right\} \equiv \left[\left(\frac{1}{|\widehat{\mathscr{C}_1}|} i\widehat{\mathscr{C}_1}\{\widehat{\sum} i - \frac{1}{|\widehat{\mathscr{C}_2}|} i\widehat{\mathscr{C}_2}\{\widehat{\sum} i\right) - min(D), \infty\right)$. D is the set of differences in retention rate between a highest retention rate ASM and its corresponding other ASMs. The

TABLE 3 Optimal patient stratification for each brain disease

Brain disease	Patients, *n*	Optimal patient stratification	Retention rate increase overall	Retention rate increase in patients with suboptimal ASM	Increase in patients with suboptimal ASM, *p*
MS	149	Split by sex, no age split	20%	27%	.048
Infection	243	Split by sex, no age split	21%	25%	.042
Dementia	699	Split by sex and by age 80 years	14%	18%	.105
Trauma	265	Split by sex, no age split	21%	25%	.075
Stroke	5024	Split by sex and by ages 60, 70, 80, and 90 years	14%	16%	<.001

Abbreviations: ASM, antiseizure medication; MS, multiple sclerosis.

idea is that if ϕ is smaller than a specific value, the clusters will have been pushed together so close that at least one pair of strata has passed each other, and the clusters will no longer consist of the same data points. 100000 samples of ϕ were drawn to estimate each p-value.

2.5 | Ethical permission

The study was approved by the Swedish Ethical Review Authority (approval number 2020–01829). All handling of personal data was done in agreement with Swedish data protection laws.

3 | RESULTS

3.1 | Validation of registry-derived ASM retention rates

Our method was based on a prescription renewal grace period of 12 months and ASM discontinuation set to 3 months after the last dispensation. We verified the validity of these assumptions by assessing retention rates of ASMs for varying time intervals of renewal, showing large shifts in retention rate rank for shorter time intervals than 12 months and little effect beyond 12 months (Figure 1D), suggesting that 12 months is a reasonable grace period.

Next, KM estimates of the retention rates of ASMs were compared to the randomized clinical trial SANAD, the largest randomized controlled trial in focal epilepsy, the kind of epilepsy in our datasets, to date.[27] Our first-line ASM retention rates for the full population were similar to those of SANAD; lamotrigine had the highest retention rate and carbamazepine had a significantly lower retention rate both after 1 year and after 5 years ($p < .001$; Figure 1E). Topiramate had a lower retention rate than carbamazepine in SANAD, but the number of patients taking topiramate in our material was too low for comparison. We also conducted sensitivity analyses with a population matched more closely to that of SANAD with only stroke, trauma, and infection within ages 20–60 years (Figure S1), and all brain diseases except stroke (Figure S2), which yielded similar retention rates for lamotrigine and carbamazepine.

The analyses have been condensed into web-based software, which allows visualization of the dataset regarding first-line ASM and the second-line ASM for individuals who tried a particular first-line ASM (Appendix S1).

3.2 | Optimal stratification and ASM selection for maximal retention rate increase

We quantified the potential for improvement of first ASM retention rates, had all patients received the ASM with the

highest retention rate for their subgroup as initial monotherapy, by determining the optimal stratification of sex and age for each brain disease with regard to retention rate improvement (Table 3). There was a potential increase in the 5-year retention rate in each of the diseases (increase in percentage points): MS, 20%; brain infection, 21%; dementia, 14%; trauma, 21%; stroke, 14% (Figure 2A). The potential increase for the group of patients using a suboptimal treatment—the difference in retention rate between the highest retention rate ASM and all other ASMs combined—was for each disease: MS, 27% ($p = .05$); brain infection, 25% ($p = .04$); dementia, 18% ($p = .10$); trauma, 25% ($p = .07$); stroke, 16% ($p < .001$). An example of stratification is patients with trauma, where optimal stratification was based on sex. Males had a higher retention rate with levetiracetam (75%, 95% CI = 54–87) than with all other ASMs (43%, 95% CI = 34–53). Females had a higher retention rate with lamotrigine 70% (95% CI = 33–89) than with all other ASMs (48%, 95% CI = 34–60).

3.3 | Posttraumatic epilepsy and epilepsy in dementia

We studied ASM treatment of epilepsy after traumatic brain injury and epilepsy in dementia, common forms of acquired epilepsy, for which there is currently inadequate evidence to guide treatment. In trauma, levetiracetam had a significantly higher retention rate than the most common ASM, carbamazepine ($p = .04$); carbamazepine was the most common first-line ASM ($n = 125$, 47%), followed by levetiracetam ($n = 50$, 19%), valproic acid ($n = 40$, 15%), and lamotrigine ($n = 35$, 13%). The 1-year retention rate was 80% (95% CI = 65–89) for levetiracetam, 77% (95% CI = 60–88) for lamotrigine, 65% (95% CI = 48–78) for valproic acid, and 62% (95% CI = 52–70) for carbamazepine. No differences other than that between levetiracetam and carbamazepine were statistically significant.

For epilepsy in dementia, levetiracetam and lamotrigine were significantly better than carbamazepine, with $p = .006$ and $p = .01$, respectively. The most common first-line ASM was levetiracetam ($n = 290$, 41%), followed by carbamazepine ($n = 182$, 26%), lamotrigine ($n = 108$, 15%), valproic acid ($n = 95$, 14%), and oxcarbazepine ($n = 12$, 2%). The 1-year retention rates were 77% (95% CI = 68–84) for lamotrigine, 74% (95% CI = 68–79) for levetiracetam, 67% (95% CI = 56–76) for valproic acid, 61% (95% CI = 53–68) for carbamazepine, and 50% (95% CI = 21–74) for oxcarbazepine (Figure 3B).

3.4 | Previously failed ASM provides information about the efficacy of the next ASM

Finally, we asked whether the first failed ASM influenced retention rates of the second ASM. This analysis was only possible in the larger brain disease cohorts, and for the more common drugs. We show an example where the rank of two ASMs is changed based on this conditioning. For initial therapy in poststroke epilepsy, lamotrigine had a higher 1-year retention rate, 84% (95% CI = 80–87), than levetiracetam, 78% (95% CI = 75–82), $p = .03$, but in patients with stroke who used valproic acid as their first ASM, levetiracetam had a higher retention rate, 93% (95% CI = 86–97), than lamotrigine, 73% (95% CI = 61–82), $p = .002$.

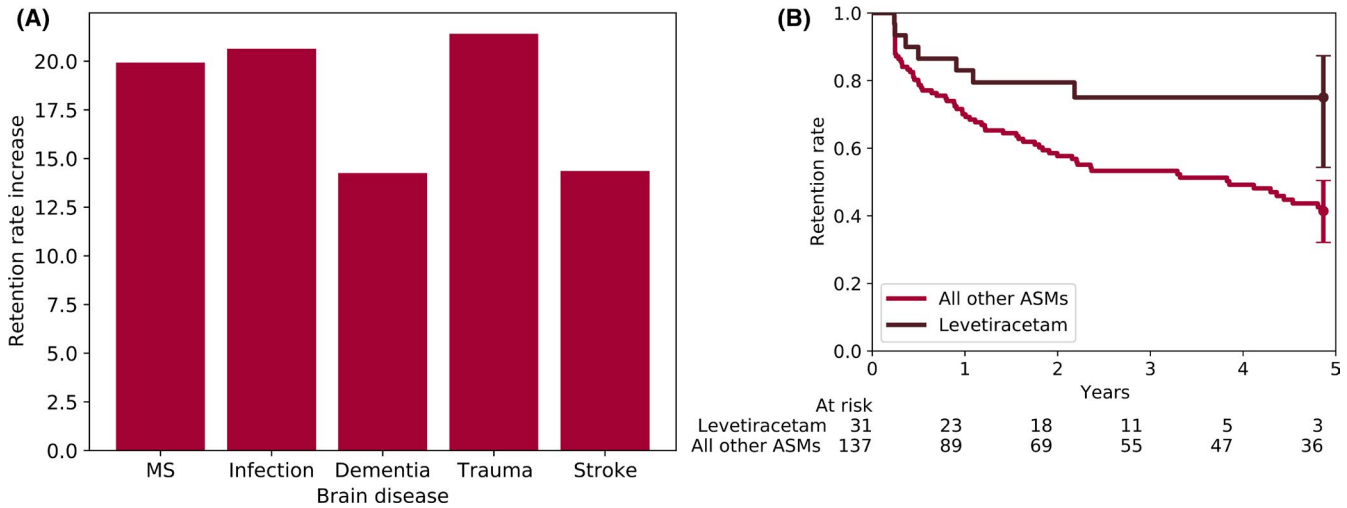

FIGURE 2 (A) The estimated increase in 5-year retention rate by using the antiseizure medication (ASM) with the highest retention rate for every patient stratification. (B) Retention rates of ASMs for males with trauma. Levetiracetam, which had the highest retention rate, is compared to the Kaplan–Meier curve of the events of all other ASMs. MS, multiple sclerosis

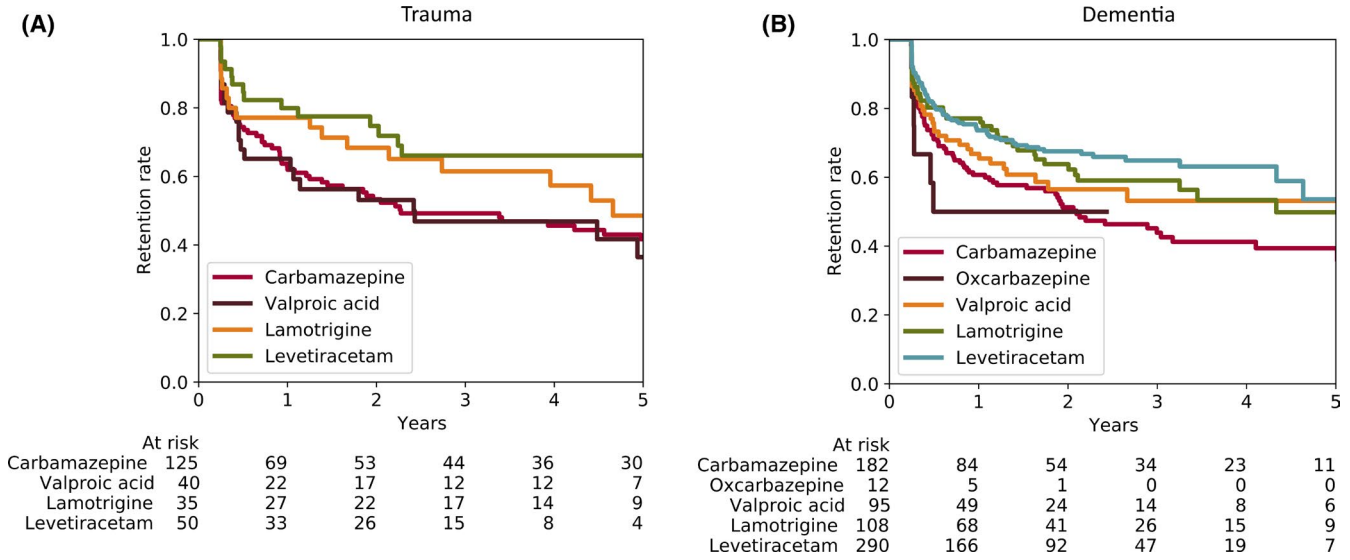

FIGURE 3 (A) Posttraumatic epilepsy. (B) Epilepsy after dementia. Number at risk is given below each graph

4 | DISCUSSION

In this nationwide study on data from comprehensive health registers, we found a potential improvement in retention rate of the first ASM of 14%–21% in patients with epilepsy in a range of brain diseases. This indicates that the application of personalized medicine—basing treatment decisions on statistics derived from representative patient groups—has significant potential in epilepsy care, and that better use of available ASMs could significantly improve outcome. We also found different retention rates of ASMs for patients with different brain diseases, which supports the clinical relevance of the 2017 ILAE classification of epilepsies, introducing etiology as a separate classification axis.[28] We also demonstrate that data from national registers offer a feasible and powerful way of determining retention rates for different ASMs based on individual patient characteristics. Although observational data can never replace randomized evidence, it is unlikely that evidence on retention rates for specific patient groups will emerge from randomized controlled trials, which often struggle to recruit a sufficient number of patients to demonstrate overall efficacy.

We also found that ASM history is of importance when selecting a new treatment. Although it is often emphasized in clinical practice, there are few data to support this notion. Our data indicate that simply ranking ASMs based on patient characteristics and trying ASMs in that order does not take full advantage of the available data. Instead, previously failed treatments are meaningful because they reveal information about potentially unmeasured variables,[29] perhaps side effects specific to mechanism of action. This is illustrated in our example of lamotrigine having a higher 1-year retention rate than levetiracetam in the stroke population, but for patients who tried valproic acid, the order was reversed. Methodologically, our study demonstrates that national registers provide enough data to allow high-resolution stratification and the possibility to compare second-line ASMs.

There are several limitations to our study. The DR was started as late as 2005, which allows only a few years of ASM tracking, and the algorithm for ASM retention was relatively crude. However, we validated our results against data from clinical randomized trials. The determination of optimal ASM use is valid if the age distribution within each stratification is similar or if a shift in age distribution is irrelevant for the retention rate in that stratification, and if physicians prescribe ASM based on, at most, brain disease, sex, and age. Patient register data do not reveal whether a preceding brain disease actually caused the epilepsy, or why particular medications have higher retention rates in some patient subgroups. Nor do the data contain information about adjudicated seizures for a patient after a dispensed ASM or the existence of psychogenic nonepileptic seizures. Effect on seizures, clinical decisions, and side effects could all matter. For instance, in patients with previous stroke and complicated secondary vascular prophylaxis, ASMs with several drug–drug interactions may need to be replaced. In Alzheimer disease and other types of dementia, a cholinergic deficit could enhance cognitive symptoms, potentially causing anticholinergic medications such as carbamazepine and oxcarbazepine to become intolerable.[30]

The underlying datasets represent a broad range of potential causes of acquired epilepsy. Survival times between the underlying brain diseases vary substantially, which supports comparing patients only within their own etiological category for calculations of potential improvement in retention rates. It is important to note that the retention rates in our study

reflect the situation for adult onset focal epilepsy, and not other epilepsy syndromes. Furthermore, retention rate, which is an integrated measurement of efficacy and tolerability of an ASM, rests on the assumption that patients quit their treatment if and only if the treatment is ineffective or intolerable. There might be cases where seizure-free patients pause their medication to evaluate whether they can remain seizure-free without it and simultaneously avoid the side effects of the ASM. However, if the magnitude of treatment pausing is similar for all treatments, this should not affect the rank of ASMs. There might also be a discrepancy between the dispensation of the drugs and the drugs used by the patient, but we assume that this difference is small, as patients should not, in general, pick up new drugs if they are not planning to continue to use them. The retention rate is built on the assumption that clinicians prescribe treatments for 3 months at a time, and that there are at most 12 months between dispensations. The sensitivity analysis in Figure 1D shows that the retention rate for different ASMs has approximately the same ranking when the 12 months assumption is changed. Finally, there is a time lag for register-based studies. Several new ASMs such as perampanel, brivaracetam, and lacosamide have become more popular in recent years. National registers are updated continuously, which offers an opportunity to incorporate information on new ASMs continuously, but to elucidate their retention rates, future studies are needed. Because the original cohorts are population-wide, there could be some overlap between cohorts; for instance, patients with stroke may later have brain injury (trauma) and then develop epilepsy. For some of the brain diseases, particularly epilepsy in MS, we could retrieve data for only a small number of patients. This can be partly explained by our requirement of epilepsy onset after the start of the DR in 2005. Ideally, data from several countries with comprehensive registers should be combined in future analyses.

There are also strengths to our study. The comprehensive Swedish national registers allowed inclusion on a nationwide scale, which enhances the external validity of our findings. The combination of a diagnostic code for epilepsy and a prescription for an ASM has been shown to be highly specific for epilepsy,[21] and an epilepsy diagnosis in the NPR has a positive predictive value of 90% for the disease.[31] The DR is comprehensive and contains all prescriptions of dispensed drugs in Sweden, making it robust to factors influencing many clinical studies, such as patient relocation. The resulting retention rates are in agreement with those described in randomized studies on focal epilepsy such as the SANAD study of a heterogeneous population and two previous randomized clinical trials (RCTs) of poststroke epilepsy.[14,15,27] Our estimates of potential improvement of retention rates are similar to those reported in a study using machine learning on prescription data.[32] Depending on the underlying etiology, 14%–21% of patients with new onset focal epilepsy in our dataset did not receive the ASM with the highest likelihood of success for their age and sex.

Real-world data from registers could be of great complementary use for clinicians, in addition to RCT data and expert-based algorithms.[3,9,10] An exciting prospect is the potential of using register data for machine learning. Conceptually, machine learning has been demonstrated to be able to use clinical and prescription data to identify ASM treatments with the lowest likelihood of treatment change.[32] The observational nature of register data comes with challenges, but nonrandomized observations and confounding could be handled by statistical matching techniques and bounding of the confounding.[29,33,34,35] The problem of right-censored data in cohorts with high mortality was handled with the KM estimator in this study, but other methods would be needed for machine learning.[36-38] In summary, register-based analysis of ASM retention rates could be useful for personalized medicine in epilepsy.

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CONFLICT OF INTEREST

J.Z. has been a speaker at nonbranded educational events organized by Eisai and UCB, and as an employee of Sahlgrenska University Hospital (no personal compensation) he is or has been an investigator in clinical trials sponsored by Bial, UCB, SK life science, and GW Pharma. None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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